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APPLICATION NO	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.

EXAMINER	
ART UNIT	PAPER NUMBER
	4

DATE MAILED:

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No.	Applicant(s)	
	09/591,737	CURIEL ET AL.	
	Examiner	Art Unit	
	Janice Li	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-56 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) _____ is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☒ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ b)☐ Some * c)☐ None of:

1. Certified copies of the priority documents have been received.
2. Certified copies of the priority documents have been received in Application No. _____.
3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

15)☐ Notice of References Cited (PTO-892)

16)☐ Notice of Person's Patent Drawing Review (PTO-948)

17)☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____

18)☐ Notice of Informal Patent Application (PTO-152)

20)☐ Other

DETAILED ACTION

Claims 1-56 are pending in the application and under current examination.

Oath/Declaration

The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP § 602.01 and 602.02.

The oath or declaration is defective because it does not identify the instant application; and each copy of the oath fails to list all of the inventors.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-3, 5-56 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The methodology for determining adequacy of Written Description to convey that applicant was in possession of the claimed invention includes determining whether the

is complete as evidenced by drawings or determining whether the invention has been set forth in terms of distinguishing identifying characteristics as evidenced by other descriptions of the invention that are sufficiently detailed to show that applicant was in possession of the claimed invention (*Guidelines for Examination of Patent Applications under 35 U.S.C. § 112, p 1 "Written Description" Requirement;* Federal Register/ Vol 66. No. 4, Friday, January 5, 2001; II Methodology for Determining Adequacy of Written Description (3.)).

Claim 1 recites "*a component recognizing CD40 antigen*", given the broadest reasonable interpretation, the claim embraces a genus of molecules that could recognize CD40 antigen, such as various anti-CD40 antibodies, and CD154 molecule. However, the component disclosed in the specification is two particular antibodies for murine and human CD40, G28.5 and FGK45. No prior art of record or the specification discloses how many and what kind of molecules the claim would encompass, and how to identify such molecules. The specification has not set forth in terms of structural or distinguishing identifying characteristics as evidenced by other descriptions of the invention that are sufficiently detailed to show that applicant was in possession of the claimed genus of the invention.

Claim 2 recites a *fragment* of a first or a second antibody, given the broadest reasonable interpretation, the claim embraces a genus of fragments having binding ability of a particular antibody. However, the only species discloses in the specification is a particular "Fab-CD40" for the first antibody, and a "anti-beta 1 integrin" for the

characteristics of the genus of the first and the second antibodies. It is well known in the art, that the proper function of antibodies is determined by the three dimensional structure of proteins. It is unpredictable without the undue experimentation to determine which fragment of the certain antibody would function properly.

Claim 2 further recites a *fiber-knob protein* of the adenovirus. Given the broadest reasonable interpretation, the claim embraces a genus of fiber-knob proteins. There are many types of adenoviruses, each type has its own fiber-knob proteins, and each protein could generate more than one antibody, and fragments thereof, targeting different epitopes of the protein. However, the only anti-fiber-knob antibody discloses in the specification is the beta 1 integrin, the specification fails to teach whether a structural-function relationship is present between the disclosed species and the genus of all anti-fiber-knob antibodies. In view the state of the art of virology and antibody production, it would require undue experimentation for one skilled in the art to practice the claimed invention.

Claim 31 recites "wherein the *modification* targets said vector to CD40". Given the broadest reasonable interpretation, the claim embraces all potential genetic modifications that would resulting in a CD40 targeting vector. However, the specification only discloses a Fab-CD40 conjugated adenoviral vector and a CD40L expressing Adv. The specification dose not disclose a common structural characteristics that would allow any person skill in the art to identify all modifications to adenoviruses, and to recognize that the applicant is in possession of the invention as it is broadly claimed.

Claim 32 recites two protein moieties, the first initiates and maintains the trimeric configuration of the fiber protein, and the second serves as a receptor-specific cell-binding ligand. Given the broadest reasonable interpretation, the claim embraces a genus of the first and a genus of the second protein moieties having recited functions. However, the only first protein moiety discloses in the specification is a particular bacteriophage fibritin, bacteriophage T4 fibritin (working example 5). Claim 33 recites a bacteriophage fibritin, which itself also embraces a genus of bacteriophage fibrin. In view of the state of the art, the fiber protein of adenoviruses is not completely characterized. It is known that the fiber protein has three domains. The head or C-terminal domain is thought to contain the binding region, but the exact location of the binding region is unknown. Moreover, it is unclear exactly what modifications can be tolerated in this region and still allows trimerization, which is necessary for internalization of the virus particle into the cell. Modification at the genetic level in turn effects the sequence of the encoded protein which may or may not effect the folding /binding properties of the protein depending upon the particular modification. Determination of the effects of particular modifications is not predictable until they are actually made and used, hence resulting in a trial and error situation.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The

specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116).

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481, 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

In analyzing whether a written description requirement is met for the claimed subject matter as a genus, a representative number of species has to be disclosed by their complete structure and other relevant identifying characteristics, such as biological functions. In view of these considerations, a skilled artisan would not have viewed the teachings of the specification as sufficient to show that the applicant was in possession of the claimed invention commensurate to its scope because it does not provide adequate written description for the broad class of *all* molecules that recognizing CD40 antigen, all antibodies that recognizing all fiber-knob proteins of adenoviruses, all protein moieties that initiates and maintains trimeric configuration of the fiber protein and all protein moieties that could serve as a receptor-specific cell-binding ligand. Therefore, only the described CD40 antibody G28.5 and anti-fiber-knob antibody FGK45, and the particular bacteriophage fibrin (SEQ ID No:1) meet the written description provision of 35 U.S.C. §112, first paragraph.

Claims 1-56 are rejected under 35 U.S.C. 112, first paragraph, as containing

one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

There are many factors to be considered when determining whether the disclosure satisfies the enablement requirements and whether undue experimentation would be required to make and use the claimed invention (see *In re Wands*, 858 F. 2d 731, 737, 8 USPQ 2d 1400, 1404, 1988). These factors include but are not limited to the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability of the art, the breadth of the claims, and amount of direction provided.

The claims recite "a gene delivery system for the genetic manipulation of immune system cells". However, the recited system targeting CD40 antigen, thus, it seems that only the cells bearing a CD40 antigen could be manipulated. The specification fails to provide an enabling disclosure as to whether all cells of immune system could be manipulated by the system.

Claims 2-4 are drawn to a gene delivery system comprising an adenoviral vector, a component recognizing CD40 antigen comprising a Fab-CD40 antibody and an antibody against fiber-knob protein of the adenovirus, wherein the two antibodies genetically fused together. Claims 32 and 33 are drawn to a gene delivery system comprising an adenoviral vector, a first protein moiety initiates and maintains the trimeric configuration of the fiber protein, and a second protein moiety serves as a receptor-specific cell-binding ligand. However, the specification fails to disclose such a two-antibody modified Adv system or two-protein modified Adv system. The

system and a beta-1 integrin antibody modified system. In working example 7, CD40L molecule serves the function of both protein moieties. The specification fails to support the instant claims because it would be unpredictable to make a two-protein modified system. This is because the state of the art in protein chemistry is probably one of the most unpredictable areas of biotechnology. The proper function of the antibodies and protein moieties depend on their three-dimensional structures of the antibody binding region, and the interactions between these three dimensional structures. Modification at the genetic level in turn effects the sequence of the encoded protein, which may or may not effect the folding/binding properties of the protein depending upon the particular modification. Determination of the effects of particular modifications is not predictable until they are actually made and used, hence resulting in a trial and error situation. Although conjugating or modifying the adenoviral vector with one molecule enhances the targeted delivery, it would be unpredictable what would occur with a two-antibody modifying system or two-protein moiety modification, it would be unpredictable whether each one of the molecule would function properly, whether the resulting effect would be synergetic. It would have required undue experimentation for one skilled in the art to make and use the instantly claimed invention.

The claims further read on a genetic modification system for *in vivo* gene targeting for immune system cells. While progress has been made in recent years for gene transfer *in vivo*, vector targeting to desired cells and tissues *in vivo* continues to be unpredictable and inefficient as supported by numerous teachings available in the art.

vectors available for *in vivo* gene therapy, and conclude that "for the long-term success as well as the widespread applicability of human gene therapy, there will have to be advances...targeting strategies outlined in this review, which are currently only at the experimental level, will have to be translated into components of safe and highly efficient delivery systems" (page 198, column 1). *Verma* (Nature, Sept. 1997, Vol. 389, pages 239-242) reviews vectors known in the art for use in gene therapy and discusses problems associated with each type of vector. The teachings of Verma indicate a resolution to vector targeting has not been achieved in the art (see entire article).

These claims further read on a gene therapy method in humans. With respect to the claim breadth, the standard under 35 U.S.C. §112, first paragraph entails the determination of what the claims recite and what the claims mean as a whole. Claim 6 recites "a therapeutic gene", claim 7 recites a list of antigens, claims 12, 15, 19, 41, 44 and 54 recite a list of diseases that use the gene delivery system for treatment, claims 18, 23, 40, 43, and 53 recite immunotherapy, dendritic cell-base immunotherapy and vaccination. Concerning the breadth of the claims, these claims clearly state an intended use as therapeutic methods. When analyzing the enabled scope of the claims, the intended use is to be taken into account because the claims are to be given their broadest reasonable interpretation that is consistent with the specification. A therapeutic method is set forth to prevent, diagnose, alleviate, treat, or cure a disease in human, therefore, will be evaluated by the standard. As such, the broadest reasonable interpretation of the claimed invention properly encompasses gene therapy for cancer,

However, the specification does not provide an enabling disclosure to support the full scope of the claims.

In view of the guidance provided, the specification discloses a CD40 targeting vector *in vitro* in cultivated cells or *in vivo* in a mice tumor model. However, the specification does not provide any evidence that the method would be effective for any type of disease listed in the claim, and in humans.

In view of the state of the art in gene therapy for human, *McCluskie et al* (Mol Med 1999 May;5:287-300) teach "UNFORTUNATELY, THE PROMISING RESULTS IN ANIMAL MODELS HAVE NOT BEEN REALIZED IN HUMAN TRIALS AND CONSIDERABLE EFFORT IS NOW BEING FOCUSED AT UNDERSTANDING THIS DIFFERENCE AND DEVELOPING WAYS OF IMPROVING THE EFFICACY OF DNA VACCINES." (See 1st paragraph of the introduction) "HOWEVER, THE RESULTS IN MICE WERE NOT ALWAYS PREDICTIVE OF THOSE IN MONKEYS AND THIS IS LIKELY TRUE FOR HUMANS AS WELL. OPTIMAL DOSE AND IMMUNIZATION SCHEDULE WILL MOST LIKELY VARY BETWEEN SPECIES. IT IS NOT CLEAR WHETHER RESULTS IN NON-HUMAN PRIMATES WILL BE PREDICTIVE OF RESULTS IN HUMANS, THUS ADDITIONAL STUDIES ARE REQUIRED." (See abstract) Applicant is reminded of numerous factors complicating gene therapy, which have not been shown to be overcome by routine experimentation or resolved using animal models or *in vitro* studies. These factors include the fate of the nucleic acid itself (volume of distribution, rate of clearance, the fraction taken up by the target cell population, the trafficking of the genetic material within cellular organelles, the rate of degradation etc.), the *in vivo* consequences of altered gene expression and protein [illegible] of the mRNA, the amount and stability of the protein produced, the

differ dramatically based on the nucleic acid used, the protein being produced, the organs and tissues involved and the disease being treated. (*Eck et al*, pg81, col 2, paragraph 3, and page 82, col. 1, paragraph 2). *Boucher et al* (J Clin Invest 1999 Feb; 103:441-5) review that host cell resistance to foreign gene is another difficulty for successful gene therapy. "DESPITE AN IMPRESSIVE AMOUNT OF RESEARCH IN THIS AREA, THERE IS LITTLE EVIDENCE TO SUGGEST THAT AN EFFECTIVE GENE-TRANSFER APPROACH FOR THE TREATMENT OF CYSTIC FIBROSIS LUNG DISEASE IS IMMINENT. THE INABILITY TO PRODUCE SUCH A THERAPY REFLECTS IN PART THE LEARNING CURVE WITH RESPECT TO VECTOR TECHNOLOGY AND THE FAILURE TO APPRECIATE THE CAPACITY OF THE AIRWAY EPITHELIAL CELLS TO DEFEND THEMSELVES AGAINST THE PENETRATION BY MOIETIES, INCLUDING GENE-THERAPY VECTORS, FROM THE OUTSIDE WORLD." Thus, it would require undue experimentation for any person skilled in the art to practice the claimed invention in humans.

Therefore, it is evident that at the time of the invention, the gene therapy practitioner, while acknowledging the significant potential of nucleic acids gene therapy, still recognized that such therapy was neither routine nor accepted, and awaited significant development and guidance for its practice. Therefore, it is incumbent upon applicants to provide sufficient and enabling teachings within the specification for such therapeutic regimens. In summary, the teachings and guidance present in the specification, as a whole, represent an initial investigation into the feasibility of the development of a useful means for gene targeting *in vivo*, which awaits further development to the practical level. Based upon the limited disclosure, the

[illegible] and the breadth of the claims, one of skill

in the art would have been required to perform undue experimentation to practice the invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention

Claim 4 is vague and indefinite because it recites two customer names of anti-CD40 antibody. The antibody should be identified by its ATCC accession number or by its amino acid sequence identification.

The recitation "a fragment thereof" (claims 2-4) is vague and indefinite because the lower limit of "fragment thereof" is not specified.

The recitation "genetic manipulation is selected from the group consisting of transduction, immunomodulation and maturation" (claims 5, 35, and 48) is vague and indefinite, because it is not clear how genetic manipulation relates to immunomodulation and the subject of the maturation.

Claims 11, 14, 17, 21, 40, 43, 53, and 54 recite the limitation "such treatment". There is insufficient antecedent basis for this limitation in the claim.

Claims 11-30 are vague and indefinite because the claims are incomplete. The methods of the claims are directed to genetically manipulating immune system cells, for

administration relates to recited effects. Method claims need not recite all operating details but should at least recite positive, active steps so that the claims will set out and circumscribe a particular area with a reasonable degree of precision and particularity and make clear what subject matter that claims encompass as well as make clear the subject matter from which others would be precluded, *Ex parte Erlich*, 3 USPQ2d 1011 at 6.

Claims 32 and 46 recites the limitation "the fiber" in line 2. There is insufficient antecedent basis for this limitation in the claim.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 5-7, 9-11, 13, 14, 16-18, 20-22, 24-31, 34-37, 40, and 42 are rejected under 35 U.S.C. 103(a) as being unpatentable over *Mendoza et el* (J Immunol 1997 Dec;159:5777-81), in view of *Christ et al* (Immunol Lett 1997 Jun;57:19-25).

These claims are directed to a gene delivery system and method of using such. The system comprising an adenovirus, a therapeutic gene, and a component recognizing CD40 antigen, wherein the therapeutic gene encodes an antigen, wherein [illegible] transduction, wherein targeting cells is dendritic cells, wherein the

method comprising administering the system to an individual in need of by systemic delivery or intradermal delivery.

Mendoza et al teach a transgene antigen delivery system comprising CD40L (recognize CD40 antigen), and the use of such system for transducing dendritic cells via intradermal and intramuscular injection. *Mendoza et al* teach that the method selectively activates CD40-bearing antigen presenting cells. "THE EFFECTIVENESS OF PCD40L IN AUGMENTING IMMUNE RESPONSE TO A TRANSGENE AG ARGUES IN FAVOR OF THE MODEL PROPOSING THAT THE TRANSGENE AG IS PRESENTED BY CD40 BEARING *APC*S...". *Mendoza et al* do not teach an adenoviral vector encoding CD40L. However, before the effective filing date of the instant application, *Christ et al* teach gene therapy with recombinant adenovirus. *Christ et al* teach "HUMAN ADENOVIRUSES HAVE BEEN THE FOCUS OF CONSIDERABLE ATTENTION AS GENE TRANSFER VECTOR DUE TO THEIR ABILITY TO EFFICIENTLY INFECT A WIDE VARIETY OF CELL TYPES BOTH IN VITRO AND IN VIVO...THE ABILITY OF E1-DELETED VECTORS TO EFFICIENTLY TRANSDUCE IN VIVO BOTH DIVIDING AND QUIESCENT CELLS FROM VARIOUS ORGANS, ... AND TO EXPRESS THE INSERTED TRANSGENE AT HIGH LEVELS...".

Obviously, using CD40L to transduce dendritic cells for enhancing immune responses of genetic vaccination is known in the art as taught by *Mendoza et al*; using recombinant adenoviral vector as a gene delivery system has also become a focus of attention for gene therapy practitioner as taught by *Christ et al.* One of ordinary skill in the art would have been sufficiently motivated to incorporate the methods of *Mendoza et al and Christ et al.*, for purpose of enhancing specific immune responses to genetic

No claim is allowed. Claims 2-4, 8, 12, 15, 19, 23, 32, 33, 38, 39, 41, 43-56 are free of cited prior art of record, because the cited prior art of the record fails to teach a system with an anti-CD40 and an anti-fiber knob antibody, and further fuse the two antibodies together genetically, or to use the particular antibody combinations; and the cited prior art of record fails to teach or fairly suggest to modify adenoviral vector with a combination of bacteriophage T4 fibritin molecule and CD40 ligand molecule. However, these claims are subject to other rejections.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Q. Janice Li whose telephone number is 703-308-7942. The examiner can normally be reached on 8:30 am - 5 p.m., Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Karen M Hauda can be reached on 703-305-6608. The fax numbers for the organization where this application or proceeding is assigned are 703-308-8724 for regular communications and 703-308-4242 for After Final communications.

Any inquiry of formal matters can be directed to the patent analyst, Kay Pinsky, whose telephone number is (703) 305-3553.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-1235. The faxing of such papers must conform to the notice published in the Official Gazette 1096 OG 30 (November 15, 1989).

Q. Janice Li
Examiner
Art Unit 1632

QJL
June 18, 2001

ROBERT A. SCHWARTZMAN
PRIMARY EXAMINER